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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,291	LAPIDOT ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *1-16 and 26-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-25 and 41-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 16 August 2010.

Claim Status

Claims 1-47 are pending. Claims 21 is amended. Claims 1-16 and 26-40 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR § 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 17-25 and 41-47 are under current examination.

Priority

This application claims benefit as a 371 of PCT/IL04/01018 (filed 11/08/2004). This application also claims benefit from foreign application ISRAEL 158868 (filed 11/13/2003). The instant application has been granted the benefit date, 13 November 2003, from the foreign application, ISRAEL 158868.

RESPONSE TO ARGUMENTS

35 USC § 112, 2nd

The rejection of claim 21 under 35 USC 112, 2nd paragraph is withdrawn in response to the applicants claim amendments. The applicant has amended claim 21, changing "immature primitive progenitors" to "stem cells." This amendment clarifies the antecedent basis from claim 17. There is perfect clarity regarding this claim language. Therefore, the examiner hereby withdraws the rejection of claim 21 under 35 USC 112, 2nd paragraph.

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 17-23 remain rejected under 35 U.S.C. 102(a) as being anticipated by Cartier-Lacave (WO03/047635, published 12 June 2003) and/or under 35 U.S.C. 102(e) as being anticipated by Cartier-Lacave et al. (US2005/0163760) for the reasons of record and the comments below.

The applicant's arguments and claim amendments have been fully considered but are unpersuasive.

The applicant has amended claim 21, changing “immature primitive progenitors” to “stem cells.” This amendment has no effect on the pending rejection, since the cited art teaches “stem cells.”

The applicant argues that the stem cells of Cartier-Lacave fail to “[exhibit] improved CXCR4 signaling capability in response to low and/or high concentrations of SDF-1” (Remarks, filed 8/16/2010, page 9, parag.2). As the term, “improved” is a relative term, and it is evident that the stem cells of Cartier-Lacave have a receptor for

SDF-1, and the applicant has failed to show that the stem cells of Cartier-Lacave demonstrate the vague functional limitation, the examiner finds the applicant unpersuasive.

The applicant further argues that "those cells [i.e., the stem cells of Cartier-Lacave] do not, and cannot, exhibit improved CXCR4 signaling capability as expressly recited in claim 17" (Remarks, filed 8/16/2010, page 9, parag.3). The applicant has failed to positively recite how a stem cell would exhibit improved CXCR4 signaling capability. Therefore, the cells of Cartier-Lacave, lacking any evidence of the contrary and having the claimed structural requirements must inherently exhibit improved CXCR4 signaling capability. The examiner has provided a rationale tending to show inherency (i.e., the evidence of an SDF-1 receptor on the stem cells of Cartier-Lacave). It is the applicant's obligation to demonstrate that this functional limitation is not met. MPEP2112(V). Accordingly, the examiner finds the applicant's argument unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 17-23 under 35 U.S.C. 102(a) as being anticipated by Cartier-Lacave (WO03/047635, published 12 June 2003) and/or under 35 U.S.C. 102(e) as being anticipated by Cartier-Lacave et al. (US2005/0163760).

The examiner reiterates the pending rejection:

Claims 17-23 are rejected under 35 U.S.C. 102(a) as being anticipated by Cartier-Lacave (WO03/047635, published 12 June 2003) and/or under 35 U.S.C. 102(e) as being anticipated by Cartier-Lacave et al. (US2005/0163760).

Claim 17 is directed to an isolated population of human cord blood or bone marrow stem cells comprising a transgene encoding CXCR4 and exhibiting improved CXCR4 signaling capability in response to low and/or high concentration of SDF-1. Cartier-Lacave et al. teach hematopoietic progenitor or stem cell capable of expressing a polypeptide selected from…a mutated form of CXCR4 (parag.0033). Cartier-Lacave et al. teach that "capable of expressing a polypeptide" means genetically engineered cells comprising a nucleic acid of interest. The examiner interprets this language to mean a transgene encoding a mutant CXCR4. Cartier-Lacave et al. teach the natural ligand of CXCR4 is SDF-1 (parag.0088), thereby indicating that cells with this receptor are responsive. The examiner has provided a rationale tending to show inherency (i.e., the evidence of an SDF-1 receptor on the stem cells of Cartier-Lacave). It is the applicant's obligation to demonstrate that this functional limitation is not met. MPEP2112(V). Cord blood stem cells and bone marrow stem cells comprise hematopoietic stem cells. The teachings of the specification encompasses muteins (i.e., mutants) of CXCR4. Furthermore, the specification indicates that muteins of CXCR4 are known to skilled artisans. Accordingly, the examiner concludes a skilled artisan would view Cartier-Lacave as anticipating claim 17.

Claim 18 is directed to the isolated population of stem cells according to claim 17, wherein the stem cells are hematopoietic stem cells. Cartier-Lacave et al. teach hematopoietic progenitor or stem cell capable of expressing a polypeptide selected from…a mutated form of CXCR4 (parag.0033).

Claim 19 is directed to the population of cells according to claim 17 or 18, being capable of differentiating towards the myeloid and erythroid lineages. Cartier-Lacave et al. teach a population of hematopoietic cells capable of differentiating towards the myeloid and erythroid lineages.

Claim 20 is directed to the isolated population of stem cells according to claim 19, wherein the stem cells are $CD34^+$ hematopoietic stem cells. Cartier-Lacave et al. teach a population of human hematopoietic cells which are $CD34^+$.

Claim 21 is directed to the isolated population of stem cells according to claim 17, wherein the immature progenitors are cells are $CD34^+/CD38^{-/low}$ cells. Cartier-Lacave et al. teach a population of hematopoietic cells which are $CD34^+/CD38^-$

Claim 22 is directed to the isolated population of stem cells according to claim 21, wherein high amount of $CD34^+/CD38^{-/low}$ cells is about 1-5% of the population. Cartier-Lacave et al. teach a subpopulation of $CD34^+/CD38^{-/}$ cells that contains more primitive HSC has been identified. Preferably, human hematopoietic cells are selected as being $CD34^+$, $CD38^-$ in combination. While CD38 is expressed on 95-99% of bone marrow derived CD34+ cells, the CD38- fraction forms colonies with long term repopulating ability." (parag.0120). Accordingly, the examiner interprets the amount of $CD34^+/CD38^{-/low}$ cells to be about 1-5% of the population.

Claim 23 is directed to the isolated population of stem cells according to claim 21, wherein high amount of $CD34^+/CD38^{-/low}$ cells is at least 3% of the population. Cartier-Lacave et al. teach a subpopulation of $CD34^+/CD38^{-/}$ cells that contains more primitive HSC has been identified. Preferably, human hematopoietic cells are selected

as being $CD34^+$, $CD38^-$ in combination. While CD38 is expressed on 95-99% of bone marrow derived CD34+ cells, the CD38- fraction forms colonies with long term repopulating ability." (parag.0120). Accordingly, the examiner interprets the amount of $CD34^+/CD38^{-/low}$ cells to be at least 3% of the population.

Accordingly, Cartier-Lacave et al. anticipated the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-25 and 41-47 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Peled et al. (Science. 1999; 283: 845-848) in view of Sawada et al (J. Exp. Med., May 4, 1998; 187(9): 1439-1449) for the reasons of record and the comments below.

The applicant has amended claim 21, changing “immature primitive progenitors” to “stem cells.” This amendment has no effect on the pending rejection, since the cited art teaches “stem cells.”

The applicant's arguments have been fully considered but are unpersuasive.

The applicant traverses the pending rejection by indicating that he disagrees that CXCR4 overexpression by addition of a CXCR4 transgene is equivalent to cytokine-induced CXCR4 overexpression (Remarks, page 11, past parag.). The applicant further states, “Applicants demonstrated that stem cells comprising a CXCR4 transgene possess unexpected properties not possess by cytokine-induced cells” (Remarks, page 11, past parag.). The applicant has indicated that these “unexpected properties” are that “cells overexpressing a CXCR4 transgene are able to resist desensitization” (Remarks, page 12, first full parag.). As the pending rejection suggests “cells overexpressing a CXCR4 transgene,” the cells suggested by Peled in view of Sawada

would also have the "unexpected properties" of the claimed cells. Therefore, the examiner finds the applicant's arguments unpersuasive.

The applicant further argues that Sawada “does not disclose or suggest that human cord blood or bone marrow stem cells comprising a CXCR4 transgene could resist desensitization by SDF-1" (Remarks, page 12, last parag.). In response to applicant's argument that the references fail to show certain features of applicant’s invention, it is noted that the features upon which applicant relies (i.e., desensitization by SDF-1) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, the examiner finds the applicant's arguments unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 17-25 and 41-47 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Peled et al. (Science. 1999; 283: 845-848) in view of Sawada et al (J. Exp. Med., May 4, 1998; 187(9): 1439-1449).

The examiner reiterates the pending rejection:

Claims 17-25 and 41-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peled et al. (Science. 1999; 283: 845-848) in view of Sawada et al (J. Exp. Med., May 4, 1998; 187(9): 1439-1449).

Claim 17 is directed to an isolated population of human cord blood or bone marrow stem cells comprising a transgene encoding CXCR4 and exhibiting improved CXCR4 signaling capability in response to low and/or high concentration of SDF-1.

Peled et al. teach "up-regulation of CXCR4 expression may be useful to improving engraftment of repopulating stem cells in clinical transplantation" (abstract). Further, Peled et al. teach human cord blood and bone marrow stem cells which have high expression of CXCR4. Additionally, Peled et al. cite Sawada as teaching "overexpression of human CD4 and CXCR4 receptors on murine CD4+ T cells led to enhanced homing of these cells to the murine bone marrow" (page 846, col.3). Peled et al. teach cells exhibiting improved CXCR4 signaling capability in response to low and/or high concentration of SDF-1.

Peled do not explicitly teach an isolated population of human cord blood or bone marrow stem cells comprising a transgene encoding CXCR4. However, Peled indicate that human $CD34^{+}/CD38^{-/low}/CXCR4^{+}$ stem cells derived from cytokine cultured bone marrow or cord blood provide improved engraftment and repopulation. Further, Peled et al., by referencing Sawada, suggest that transgenic stem cells comprising a human CXCR4 gene are an alternative method of upregulating CXCR4 expression.

Sawada et al. teach a transgenic mouse comprising a human CXCR4 gene (page 1440, Materials). The transgenic mouse comprises a cell population comprising stem cells having the human CXCR4 gene. Sawada was in the possession of peripheral blood, cord blood, and bone marrow from a transgenic mouse comprising stem cells having a transgene encoding human CXCR4 (e.g., Figure 3). In particular, Sawada teaches an isolated population of transgenic murine bone marrow cells comprising a human transgene encoding CXCR4 (page 1443, col.2, Discussion). It is known in the art that bone marrow contains some hematopoietic stem cells.

Claim 18 is directed to the isolated population of stem cells according to claim 17, wherein the stem cells are hematopoietic stem cells. Peled teach human $CD34^+/CD38^{-/low}/CXCR4^+$ stem cells. Peled teach that $CXCR4^+$ is expressed on hematopoietic cells.

Claim 19 is directed to the population of cells according to claim 17 or 18, being capable of differentiating towards the myeloid and erythroid lineages. Peled teach population of cells capable of differentiating towards the myeloid and erythroid lineages (page 848, col. 1, parag.1).

Claim 20 is directed to the isolated population of stem cells according to claim 19, wherein the stem cells are $CD34^+$ hematopoietic stem cells. Peled teach human $CD34^+/CD38^{-/low}/CXCR4^+$ stem cells.

Claim 21 is directed to the isolated population of stem cells according to claim 17, wherein the immature progenitors are cells are $CD34^+/CD38^{-/low}$ cells. Peled teach human $CD34^+/CD38^{-/low}/CXCR4^+$ stem cells.

Claim 22 is directed to the isolated population of stem cells according to claim 21, wherein high amount of $CD34^+/CD38^{-/low}$ cells is about 1-5% of the population. Peled teach human $CD34^+/CD38^{-/low}/CXCR4^+$ stem cells. Peled teach this limitation (see Fig.4A).

Claim 23 is directed to the isolated population of stem cells according to claim 21, wherein high amount of $CD34^+/CD38^{-/low}$ cells is at least 3% of the population. Peled teach human $CD34^+/CD38^{-/low}/CXCR4^+$ stem cells. Peled teach this limitation (see Fig.4A). Furthermore, as “the population” is not a pure population of $CD34^+/CD38^-$

$^{/low}$ cells, various methods of preparing can produce differing percentages of $CD34^{+}/CD38^{-/low}$ cells. The percentages of these markers in a population of cells are not a patentable distinction. Therefore, the examiner concludes that an isolated population of stem cells which have some percentage $CD34^{+}/CD38^{-/low}$ cells would be deemed obvious by a skilled artisan.

Claims 24-25 are directed to limitations which affect the concentration of SDF-1, which can be used to stimulate the claimed isolated stem cell population. These claims do not further limit the structure of the isolated stem cell population of claim 1; rather they describe a characteristic of the cells under certain manipulated conditions. However, Peled teach that various concentrations of SDF-1 can be used to stimulate the claimed isolated stem cell population (see page 846, Fig.2 and page 848, reference 23).

Claims 41-47 combine limitations from claims 22-25, regarding the % population and concentrations of SDF-1. These are obvious variants of the teachings taught by the cited art.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Peled and Sawada to make an isolated population of human cord blood or bone marrow stem cells comprising a transgene encoding CXCR4.

The person of ordinary skill in the art would have been motivated to combine the teachings of the cited art because Peled suggest that isolated stem cells with upregulated expression of CXCR4 provide improved engraftment of repopulating stem

cells. Peled and Sawada indicate that transgenic stem cells comprising a transgene encoding CXCR4 provide enhanced homing of these cells to bone marrow. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute a transgene encoding CXCR4 (as suggested by Sawada) for cytokine induction of CXCR4 (as taught by Peled) in an isolated population of human cord blood or bone marrow stem cells.

The person of ordinary skill in the art would have been motivated to substitute one known, equivalent element for another to obtain predictable results. The claimed isolated population of human cord blood or bone marrow of stem cells comprising a transgene encoding CXCR4 would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. In the instant case, it would have been obvious to substitute CXCR4 transgene overexpression in isolated human cord blood or bone marrow stem cells for cytokine induced CXCR4 overexpression in isolated human cord blood or bone marrow stem cells because Peled et al teach the equivalency of the methods of CXCR4 overexpression for producing stem cells with enhanced homing to bone marrow.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Peled et al. and Sawada et al. because Sawada teach successfully making transgenic murine stem cells having a human CXCR4 gene. Therefore, making transgenic human stem cells having a human CXCR4 gene would

likely be successful. There is nothing of record or in the art that suggests this would be difficult.

Therefore the isolated population of human cord blood or bone marrow stem cells comprising a transgene encoding CXCR4 as taught by Peled et al. in view of Sawada et al. would have been *prima facie* obvious over the isolated population of human cord blood or bone marrow of stem cells of the instant application.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SCOTT LONG/
Primary Examiner, Art Unit 1633